CRITICAL REVIEW

THE PATHOLOGY OF APOPLEXY

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THE problem of the apoplectic insult presents difficulties which are typical of those met in all investigations in pathological anatomy. While the apoplexy itself is one of the most striking and dramatic events in clinical medicine, the anatomist has to draw his conclusions from a static fixed picture and to reconstruct the process in all its stages from the comparison of a great number of different final states. No wonder that the interpretations are never conformable and reflect the historical development of physiological and pathological knowledge. It is still more surprising that, as shall be seen, not only the interpretations but even the facts of observation differ so largely with different investigators. This incongruity is caused to a certain extent by a confusion in terminology, so that different authors obviously apply the same term for different things or different terms for the same thing. Therefore it is necessary to summarize briefly what is more or less generally accepted as the anatomical equivalent of apoplexy. Three different kinds of lesions can be sharply distinguished. First, there is the massive hæmorrhagic apoplexy in which is found a more or less massive hæmorrhage in one or several areas of the brain. Often from the area in which the hæmorrhage occurs a solid clot is easily separated and falls out on section, leaving behind a cavity with hæmorrhagic walls. Secondly, there is the softening, an area which does not show hæmorrhage but a diminished consistency and slight or more pronounced shrinking or discoloration of the tissue. Thirdly, there is the hæmorrhagic infarction, which presents a picture similar to the softening and distinguished from it only by the extravasation of blood into the softened area, usually in innumerable small stipples. A great deal of confusion in the more recent literature is due to the fact that a distinction is not always clearly drawn between the first and the last types, namely, the apoplectic hæmorrhage and the hæmorrhagic infarction. As at least one of these three types of lesion is the usual finding in cases which clinically present the picture of apoplexy, we may regard them as the anatomical basis of this process. However, in a large number of such cases one finds other additional lesions, small foci of necrosis and scar formation in the basal ganglia (*état criblé, état lacunaire*), and in the cortex. As these smaller areas of necrosis differ from the large areas of softening only in size, it seems to be obvious that they represent the anatomical equivalent of short transitory attacks of fainting, giddiness, aphasia, blindness, or paresis which may occur in those patients.

In addition to the three chief types, one ought to mention certain cases which Westphal (1926) has brought into prominence. These were cases which showed the typical clinical picture of apoplexy but failed to show any anatomical lesion. As a microscopical examination in these cases was not done or was incomplete, it is possible that these cases presented only early stages of necrosis which are macroscopically undiscovered and would be revealed on exact histological examination. Therefore these doubtful cases may be eliminated from our consideration.

Vessel Lesions as the Causes of Cerebral Hæmorrhage in Arteriosclerosis and Hypertension

In reading the description of cases, it is quite evident that most of the anatomical investigations on apoplexy deal with the first-mentioned type, the apoplectic massive hæmorrhage. Until a few decades ago the pathogenesis of this disturbance seemed to be clear. Charcot's view was more or less accepted. Charcot and Bouchard (1868) had reported 77 cases of cerebral hæmorrhage, in all of which they found circumscribed small swellings of the arterial branches within the brain. These miliary aneurysms were 0·2 to 1 mm. in size and had a globular or fusiform shape. Their number varied from 2 to 100 in each case. As Charcot and Bouchard saw aneurysms in the wall of the hæmorrhage or in close relationship to the hæmorrhagic area or, less frequently, somewhere in the brain and in no direct relationship to the focus of hæmorrhage, it seemed probable that the hæmorrhage was associated with these aneurysms. In order to prove that these aneurysms are really the source of hæmorrhage the actual rupture must be seen. It is therefore important to note that in only three of their cases did Charcot and Bouchard mention definite ruptures of aneurysms.

During the following years (Zenker, 1872 ; Arndt, 1878 ; Eichler, 1878 ; Rindfleisch, 1878 ; Turner, 1882 ; Monakow, 1905) Charcot's theory was accepted with certain alterations, chiefly concerning the histological nature of the aneurysms. The causal connection between the aneurysms and the hæmorrhage seemed to be evident. Löwenfeld (1886) pointed out in a thorough investigation of 17 cases of hæmorrhagic apoplexy with recent and old areas of hæmorrhage that the hæmorrhage did not necessarily arise from miliary aneurysms. He found severe changes, "simple, fatty, and granular degeneration" in the walls of the cerebral vessels in such cases. These changes, however, did not occur only within the area of hæmorrhage, although they were more marked and more frequent there than in other parts of the brain. One of his cases did not show any ruptured miliary aneurysm, but a ruptured vessel without a miliary aneurysm. In Löwenfeld's cases the rupture of the vessel wall and the mechanical injury of the brain substance by the violence of the released blood stream, thereby producing secondary ruptures of the surrounding vessels, were sufficient to explain the picture.

After Eppinger's (1887) general description and classification of aneurysms, the most thorough and exact investigation into the nature of these special aneurysmal formations was done by Pick (1910) and his collaborator Ellis (1909). They showed that these formations were not true aneurysms but either subadventitial hæmorrhages or extramural hæmatomas surrounded by fibrin, destroyed brain substance, and elements of the vessel wall itself. They are produced by the rupture of a previously normal vessel or of a vessel which has already shown dissection of its layers. According to Pick and Ellis a fatal hæmorrhage can never occur from these miliary aneurysms, and the aneurysms which actually are seen to be ruptured within the hæmorrhagic area are of a larger size than the miliary aneurysms of Charcot and Bouchard. Pick also emphasized that the tissue surrounding the miliary aneurysms never showed a marked cellular reaction ; thus it may be presumed that they did not arise a long time before death. Shennan (1915) came to a similar conclusion, namely, that a local dilatation of the diseased vessel ruptures and produces the apoplectic hæmorrhage. This local dilatation is not a pre-existent chronic change, but immediately precedes the rupture. It is also of a larger size than Charcot's miliary aneurysm. The hæmorrhage may follow the formation of a dissecting aneurysm similar to the dissecting aneurysms of the large arterial trunks. Shennan states that he found in all his cases only one single miliary aneurysm which corresponded to Charcot's and Bouchard's description. Stein (1895) had previously reported six cases of apoplexy in which an exact examination had not shown any miliary aneurysms. In some of

the vessels the adventitial space was filled with blood or detritus. Thus these findings showed even more conclusively that the classical theory of the causal significance of the miliary aneurysms in apoplectic hæmorrhage was not entirely adequate.

This was the situation when the paper by Rosenblath (1918) appeared. It formed the basis of discussion in most of the succeeding investigations, just as Charcot's and Bouchard's work had done. Rosenblath found in an exact macroscopical and histological study of 11 cases, of 2 hours' to 15 days' duration between apoplexy and death, that the hæmorrhage never occurred from one vessel but from many vessels simultaneously, that vessels and brain substance had both undergone acute necrosis in the area of hæmorrhage, and that the form of the lesion and the mode of expansion of the hæmorrhage could not be explained by the mechanical violence of the blood stream destroying the tissue. Hence he concluded that the necrosis of vessel and brain tissue was the primary event and the hæmorrhage followed into a previously necrotic area. His hypothetical explanation of this process is unlikely. He postulated that a toxic ferment produced by the contracted kidney caused the acute necrosis in the brain. This hypothesis was not accepted by succeeding investigators. Although the whole conception was a great stimulus to investigators who followed him, some of his results appear open to criticism. For instance, the presence of many punctate hæmorrhages in the periphery is no evidence that the entire lesion must have been produced by the confluence of such small hæmorrhages. The violence of a massive hæmorrhage can undoubtedly produce small punctate hæmorrhages in the neighbourhood simply by the mechanical damage to the small vessels. Similar small hæmorrhages may be found round a fresh bullet-hole in the brain (Stämmeler, 1927) or round an experimentally injected clot of chicken blood in a dog's brain (Rühl, 1927). But there seems to be a difference between these secondarily produced marginal small hæmorrhages and the small foci of hæmorrhage which are to be seen in the peripheral zone of gross apoplectic lesions. This point requires further investigation. Rosenblath argues that the form of the lesions in apoplectic hæmorrhages is very much against the view that they are produced by a bursting vessel and the mechanical destruction of the surrounding brain tissue. Actually the egg-shape of a certain type of putamen-claustrum hæmorrhage is difficult to explain by the mere mechanical force of the outflow of blood. However, in the marginal zone of other apoplectic hæmorrhages, especially in the lower brain stem, one can show that the hæmorrhage does in fact follow the planes of least resistance in the fibre network (Stern, 1935). Rosenblath maintains that the smooth walls of the hæmorrhagic cavity and the hæmorrhages which stop short immediately underneath the ventricular wall are much against the mechanical theory. Some hæmorrhages show the form of slits; there are cases in which the walls of the cavity show torn and irregular tissue (Böhne, 1927) and, as is well known, there are many cases in which the hæmorrhage actually breaks through into the ventricle.

Several important points in Rosenblath's theory have received ample proof. The source of hæmorrhage is multiple in most cases. The vessels in the entire area of hæmorrhage undergo "arterionecrosis." The expansion of the hæmorrhage cannot be explained by rupture and mechanical violence only. Lastly, the small miliary dissecting aneurysms of Charcot and Bouchard are not the cause but one of the accidental results of the process.

Lindemann (1924) confirms that there are always many vessels from which the hæmorrhage occurs and that the hæmorrhage is not so much produced by rupture as by diapedesis and "diuresis." Böhne (1927) compared the volume of both hemispheres, the hæmorrhagic and the normal hemisphere of the same brain. The volume of the apoplectic hemisphere may be a quarter more than that of the healthy one. Thus there must be a considerable displacement of brain substance by the hæmorrhage. Rosenblath had emphasized that in many cases one cannot judge by external appearances in which part of the brain the hæmorrhage had occurred and that the hæmorrhage did not obviously displace a considerable amount of brain

substance. On the other hand, Böhne's contrary statement is not against the presumption of a preceding necrosis.

Transient Disturbances of the Vessels as the Cause of Hæmorrhage and Softening

Westphal and Bär (1926) confirmed Rosenblath's findings, but tried to replace his hypothesis of a chemical noxis destroying the brain tissue by another which seemed more in accordance with clinical observations. Westphal's view is based on certain facts. Spasm of the retinal vessels has been observed occasionally in patients with arterial hypertension and in whom certain paradoxical microcapillary reactions have been observed. There was no "reactive hyperæmia," but rather angiospasm after arterial compression. Moreover, it is true that apoplexy is often preceded by minor fits which obviously do not lead to a gross hæmorrhage. From these facts, combined with the anatomical findings, Westphal draws the conclusion that in arterial hypertension a local arterial spasm producing ischæmia and necrosis preceded the hæmorrhage. This hypothesis necessitates the assumption that the cause of the necrosis of the artery is a preceding arteriospasm, and that hæmorrhage follows the arterionecrosis with subsequent tissue necrosis. Westphal mentions cases in which the clinical picture was that of a typical stroke with following paresis in a patient with arterial hypertension and in which at post mortem neither a lesion in the brain nor an obstruction of the vessels was found. In such cases a transitory ischæmia due to an arterial spasm may have produced the stroke. We have already mentioned that these cases are, at least as far as the negative findings in the brain are concerned, doubtful. Jaffé (1927) studied the vessels in the case of a gross cerebral hæmorrhage occurring in an eclamptic woman of 33 years who had a high arterial pressure and no signs of arteriosclerosis. He followed Westphal's theory. Globus and Strauss (1929) found in brains with apoplectic hæmorrhage signs of previous circulatory damage, such as scars, more recent softening, and general gliosis. From these findings they drew the conclusion that the degeneration of the surrounding brain tissue as well as vessel disease and hypertension is an important factor in the production of hæmorrhages. They even mentioned one case which "in the absence of a pre-existing cerebral softening escaped spontaneous massive hæmorrhage" though diffuse chronic disease of the cerebral vessels associated with hypertension was present. As in this case no description of the microscopical findings was given, circulatory disturbances can hardly be excluded. But even the pre-existence of disintegration of the cerebral tissue does not prove that it is a necessary condition in the production of hæmorrhage. We can only say that the same diseases which tend to produce softening and diffuse proliferative changes in interstitial tissues also lead to hæmorrhages. The immediately causal connection between the two processes postulated by Westphal is not proved.

Westphal's view is fairly typical of current opinion regarding our present subject. While in the classical literature hæmorrhage was almost identical with vessel rupture and softening with thrombosis, the conception of transient "functional" vascular disturbances has dominated recent work.

It is, however, often very difficult to differentiate clearly between unfounded conjectures and fruitful theories. Therefore it is necessary to enquire why the basis of a direct causal connection between a visible organic lesion of a vessel and the resulting brain lesion was abandoned in favour of much vaguer and less-defined conceptions. It is quite a common experience in morbid anatomy that there may be no immediate connection between the degree of arteriosclerosis on one side and the amount or number of hæmorrhages and softening on the other. One may find on the one hand extensive and numerous lesions in a brain with only slight disease of the vessels, and on the other no gross lesions in a brain with severe arteriosclerosis (Neubürger, 1930). If a comparison is made in arteriosclerotic brains between the extracerebral vessels in an area of high "vulnerability," such as the pons, and those of a very "resistant" area near to it, as the hypothalamus (Stern, 1935), the degree

of arteriosclerosis is found to be the same in both. Such observations deal only with a gross examination of extracerebral vessels. In regard to the intracerebral vessels, the occurrence of cerebral necrosis in the absence of visible obstruction is reported by a number of different observers. Foix and Hillemand (1924) report cases of cerebral softening in which serial sections of the arteries to the softened areas did not reveal the presence of either thrombosis or obliteration. Unfortunately these cases are only mentioned without details in a discussion. Spielmeyer (1924) reported cases of arteriosclerosis with necrotic areas of apparently the same age scattered all over the cortex in which the arteries supplying these areas showed no recognizable change. He speaks of "vasomotor" disturbances in cerebral arteriosclerosis. Neubürger (1926) reports an interesting case of a healthy man of 31 who, after a traumatic commotion with a lucid interval of 1 hour, developed a hemiplegia and died 2 days later. At post mortem no lesion of the skull was found; there was a softening in the area of one of the branches of the middle cerebral artery though the vessels were healthy and patent. Neubürger draws a parallel to the post-traumatic segmental arterial spasm which has been observed in living patients by surgeons (Küttner and Baruch, 1920; Vianney, 1919). In most of these surgical cases, however, a lesion of a neighbouring vein seems to have preceded the spasm of the artery. A good example is the case of Duval, Lhermitte, and Vermes (1935), in which the ligation of a jugular vein was followed by a hæmorrhagic softening on the same side. In 1927 Rosenblath described 12 cases of arterial hypertension with cerebral softenings in which he found vascular changes similar to the arterio-capillary fibrosis of Gull and Sutton (1872). But as these vascular changes were not merely confined to the areas of softening it is probable that such vascular changes were not the immediate cause of the necrosis. No other obstruction of the arteries, embolic or thrombotic, was seen. H. Spatz (1935) described a case of the cerebral form of Buerger's disease (thrombo-angiitis obliterans) in a man of 43 years. There were varying symptoms of speech disorder, mental disturbance, and transitory pareses throughout the 7 years of the illness. The anatomical examination finally revealed a proliferative endarteritis and organizing thrombosis of both carotid arteries and several of their branches, especially the left middle cerebral artery, which resulted in multiple diffuse lesions of the nervous tissue. There were similar changes in the coronary arteries. There was no evidence of true arteriosclerosis. In the clinical history there was nothing suggestive of any gangrenous disease of the limbs, though there was considerable evidence of frequent vasomotor disturbance of the extremities, such as paroxysms of coldness and lividity of hands and feet. The blood pressure was normal. From this and from the way in which the neurological and mental symptoms developed, Spatz concluded that cerebral angiospasm had preceded the organic disease of the vessels. If this was so we still do not know if the cerebral softenings did occur at a stage when the vascular disease was of a purely "functional" character. Guillain and Bertrand (1932) demonstrated a case with intact arteries in which there were symmetrical necroses of long standing in the parietal and occipital lobes. Riser (1935), in a case of cerebral softening, injected with gelatine the arteries supplying the softened area. The arteries showed some small narrowings produced by arteriosclerotic plaques, but they were otherwise patent.

From all these facts it is quite evident that necrotic lesions of the brain may occur without any associated visible obstruction (thrombosis, embolism, obliteration) of the arteries. As the shape and distribution of such lesions suggest their arterial origin, they must have resulted from transient "functional," "non-organic," or "vasomotor" disturbances. Thus for the pathogenesis of a great number of cerebral softenings the function of the vessels becomes more important than their morphological picture. This view receives further support from those cases where completely obstructed arteries have not caused any necrosis (Pagnicz, 1902; Claude and Cuel, 1927; Ley, 1931); as is well known, a slow development of the obliterative process may allow of a sufficient anastomotic supply.

The next important problem is to determine if the same or similar transient "functional" disturbances of the vessels, the nature of which is not known, can produce not only softenings but also hæmorrhages. Lampert and Müller (1925) have carried out an interesting experiment regarding the question of rupture of vessels by an increase of intra-arterial pressure. In human bodies of subjects who died with cerebral arteriosclerosis they injected fluid under a high pressure into both carotids. Only by applying pressure of 1 to $2\frac{1}{2}$ atmospheres for 6 minutes did they succeed in producing ruptures with destruction of brain substance by the leaking fluid. Such pressures never occur in human pathology. From the results of such experiments and from the histological findings of Rosenblath (1918, 1926), Lindemann (1924), Pollak and Rezek (1927), Alajouanine, Thurel, and Hornet (1936), it may be said that cerebral hæmorrhage is not likely to be the result of rupture of one or a few rigid blood vessels from a sudden increase in blood pressure.

There is no supporting fact of observation either in the brain or in any other organ for Westphal's theory of an angiospasm causing not only necrosis of the parenchyma but also necrosis of the "spastic" vessel itself. Let us eliminate the massive apoplectic hæmorrhage and consider only the hæmorrhagic infarction. By the latter is meant the necrobiotic change with intact continuity of tissue and numerous capillary hæmorrhages within the damaged area. Ricker (1924) has shown in experiments on the pancreas and ear of the rabbit that necrosis does not actually occur during the period of angiospasm and ischæmia. It occurs during the stage of prestasis when the blood stream in the precapillary and capillary bed is extremely slowed or when the blood flow has stopped and the vessels are engorged. Ricker shows that if he applied to an artery a stimulus of varying character the result to be observed in the precapillaries and the capillaries belonging to that artery was always the same. With a light stimulus angiospasm and ischæmia occurred. If he increased the strength of the stimulus the arterioles and capillaries widened and the leucocytes took up a marginal position and emigrated into the tissue through the stomata of the capillary wall; erythrodiapedesis then took place. At this stage the earliest necrotic changes of the tissue were observed. If he increased the stimulus still further stasis occurred with massive erythrodiapedesis. Ricker observed that these processes occurred constantly in the same order and that there was no difference if he applied chemical, mechanical, or thermal stimuli. He assumes that the mechanism producing these changes is nervous. It is not possible here to go into any further details of the physiology of the circulation; but even if Ricker's findings really represent an invariable "law," there are reasons enough to believe that these observations cannot immediately be applied to the human brain. With this reservation, it may nevertheless be said that Ricker's attempted explanation best meets the histological picture of ischæmic and hæmorrhagic infarctions. In infarction of the brain it is possible to see all the different stages described by Ricker in his experiments. The ganglion cells may have undergone necrobiotic changes, the capillaries being extremely engorged; or the ganglion cells and capillaries may show the same changes with the leucocytes scattered through the necrotic tissue; or the ganglion cells may be unstainable by basic aniline dyes and there may be massive erythrodiapedesis; or there may be erythro- and leucodiapedesis in a tissue in which the damaged ganglion cells are still to be seen. In other words, all stages described by Ricker in the living animal may be seen in one or other lesion found at post mortem of the human.

The necrosis in typical infarctions may be confined to a certain part of the grey matter, namely, the cortex or only the lower layers of the cortex. This sharp limitation cannot be explained by the angio-architecture, because some of the pial arteries pass through the cortex into the deep parts of the white matter. It could be explained by the higher vulnerability of the nerve cells to ischæmic noxa, a point which is so often emphasized. But the fact that the hæmorrhage in hæmorrhagic infarction is almost exactly confined to the area where the necroses occur is hardly explained in this way. If Ricker is correct in stating that the disturbance in the "terminal" vascular

area—prestasis, leucodiapedesis, erythrodiapedesis, stasis, necrosis—is due to a stimulus to the arterial trunk which is transmitted to the periphery by a nervous mechanism, it is necessary to prove that such a pathological stimulus to the arterial wall does occur. Consideration of this leads to a discussion of Schwartz's (1930) theory of the embolic lesions. Schwartz considers that the obstructive factor in embolism is not the deciding factor, because it does not explain the limitation of the small hæmorrhages to certain parts of the grey matter such as are quite common in embolic infarction. He believes that the true cause is the trauma to the arterial wall by the sudden lodgement of the embolus. This lodgement brings about a functional disturbance in the terminal distribution of the artery. This disturbance follows the same mechanism Ricker has described in his experiments. Schwartz's extensive monograph on the pathology of apoplexy is based on Ricker's theory. The result is that all lesions in arteriosclerosis, embolism, and arterial hypertension, with the exceptions of massive thrombotic obstructions in arteriosclerosis, are due to pathological stimuli to the arterial trunk which cause by a nervous mechanism circulatory disturbance in the terminal distribution. Against such an hypothesis it must once more be emphasized that the circulation in the brain is in many ways different from that in the organs Ricker has studied, and, moreover, the analogy to Ricker's different stages is only to be found in ischæmic and hæmorrhagic infarctions and not in massive apoplectic hæmorrhages such as are so common in the basal ganglia, the white matter of the cerebrum, and in the pons. The material which Schwartz demonstrates illustrates once more the inadequacy of the classical mechanical theories. His hypothesis, however, is insufficiently supported by physiological facts. The bilateral and absolutely symmetrical softenings and small hæmorrhages in the basal ganglia which he shows may possibly be explained by a nervous impulse transmitted symmetrically along the arterial tree to its terminal branches on both sides. Physiological evidence in favour of this is, however, wanting. Again, these findings are not frequent enough to give sufficient basis for such a general explanation. Schwartz stresses the morphological similarity between embolic and hypertensive lesions to prove the similarity in pathogenesis—namely, a shock to the arterial trunk producing functional disturbance in the terminal vessels. It is known that embolus is likely to pass along vessels which continue the most direct stream of blood. As the lenticulo-striate arteries come off the middle cerebral artery opposite the end of the internal carotid, emboli passing up the carotid tend to lodge in the lenticulo-striate artery. This results in embolic lesions being found chiefly in the distribution of the lenticulo-striate arteries. As Schwartz found in arterial hypertension the site of hæmorrhage or softening to be in the distribution of the lenticulo-striate artery, he postulated that a sudden rise in arterial pressure passed as a wave from the heart along the most direct route—namely, into the lenticulo-striate artery. If this hypothesis be correct, it would be expected that those branches of the basilar artery which come off in a most direct line with the stream of blood would be the site of hæmorrhage and softening in cases of hypertension. The vessels so placed are those going to supply a part of the hypothalamus including the mamillary bodies. Vascular lesions in these areas are, however, extremely rare. In fact, it should be pointed out that the site of vascular lesions is commonly in the distribution of the pontine arteries, which come off the basilar artery at a right-angle or even more acutely.

Another attempt to explain the multiple hæmorrhages in areas of infarction has been put forward by Volhard (1932). He explained the hyperæmia as reactive to the "lack of oxygen" in the ischæmic area and the diapedic hæmorrhage only as a higher degree of this reactive hyperæmia.

It is only to be expected that Westphal's and Schwartz's hypothetical conceptions were followed by investigators who either returned completely to the classical and purely mechanical view or at least restricted themselves more to the observation of visible changes and rejected all other hypotheses (Rühl, 1927; Böhne, 1927; Stämmer, 1927; Green, 1930; Wolff, 1932; Hiller, 1935). Hiller states definitely from a

study of 59 cases that a state of disintegration ("status lacunaris," "status cribrosus" of Pierre Marie (1901)) is a prerequisite for the occurrence of cerebral hæmorrhage in arteriosclerosis and hypertension. He once more stresses the difference between the massive apoplectic hæmorrhage and the hæmorrhagic infarction. These have been confused so much in the polemics of recent years. In his cases the arteries of the disintegrated areas showed changes such as intimal proliferation, hyperplasia of the mesial coat, and dilatation of the perivascular space. The nervous tissue itself showed the well-known pictures of multiple softenings of different age. Therefore Hiller assumes as important for the pathogenesis of the hæmorrhage the changes of the arteries and the diminished perivascular resistance. He also emphasizes that a massive hæmorrhage with rupture into the ventricle is never caused by the confluence of numerous small diapedic hæmorrhages. It is very interesting that he found only very few hæmorrhagic apoplexies in nephritic arterial hypertension. It is also surprising and not in accordance with the findings of previous authors that in most of his arteriohypertensive patients under 60 years he found definite anatomical signs of arteriosclerosis. But even if—as Hiller states—the arteries in areas where the hæmorrhages occur show arteriosclerotic changes, the problem is essentially the same and has only changed its aspect. Because the arteriosclerosis, especially the hyperplastic change of the media of the small arteries, is probably the result of a functional overstrain (McCallum, 1936) and because early cases of arterial hypertension may show cerebral hæmorrhage without visible change in the arteries, it is logical to assume that the mechanism which leads to the vessel disease is also the cause of the final catastrophic event. Even if the marked arteriosclerosis in the arteries of the basal ganglia and pons were the constant cause of hæmorrhages in these areas, it remains to be determined why the arteriosclerosis is limited to these areas.

The Problem of Local Vulnerability

This leads to the question of the frequency of hæmorrhages and softenings in certain areas and their extreme rarity in others. If arterial hypertension affects the vessels of all parts of the central nervous system equally, why is it that the resulting lesions are not distributed according to mathematical probability?

Ludlum (1909) studied the distribution of the gross apoplectic lesions under the immediate influence of Beevor's (1908) work. In the 91 cases reported the site of the lesion was as follows: there were seven hæmorrhages and six softenings in the area of the posterior cerebral artery, especially in the region of the thalamus; six pontine lesions in the distribution of the basilar; eight lesions in the area of distribution of the posterior communicating artery; three lesions in that part of the internal capsule supplied by the anterior choroidal artery. All the remaining 61 lesions were in the distribution of the striate arteries. The distribution of the cerebral hæmorrhages is, according to W. S. Greenfield, as follows; 75 per cent. occur in the region of the basal ganglia, 10–12 per cent. in the pons, 12 per cent. in the meninges, 1 per cent. or less in the cerebellum. Those occurring in relation to the meninges belong to a group not under discussion here. Boyd (1934) in his textbook gives a somewhat different distribution. In the order of frequency they are: (1) the area of the lenticulo-striate artery; (2) the white matter of the frontal lobe (anterior cerebral artery); (3) the pons and the cerebellum. Schwartz (1930) emphasizes that the predilective areas are similar in apoplexy associated with arteriosclerosis, arterial hypertension, and embolism. There was only one exception among his observations: the cortex was more seldom affected in hypertension than in arteriosclerosis or embolism. The areas mostly affected are the middle third of the corpus striatum and the claustrum, then the thalamus and the pons. The globus pallidus and the medulla oblongata extremely rarely showed lesions. The most common cortical lesions in arteriosclerosis and embolism were located in the insula, the operculum, the supramarginal gyrus, and the superior temporal gyrus.

If it were possible to find a common feature in the vascular supply of all the vulnerable areas or in that of the most resistant parts of the central nervous system, it would undoubtedly advance knowledge as to the pathogenesis of these lesions. Duret (1874) and Heubner (1874) early stressed the importance of the presence of extra-cerebral arterial anastomoses in explaining the resistance of certain sites to vascular lesions. Kolisko (1891) thought that the comparatively rare occurrence of such lesions in the area of the anterior choroidal artery might be explained by the acute angle at which this vessel branches off the carotid artery. But it has already been mentioned that the pontine vessels branch acutely from the basilar artery and that hæmorrhages frequently occur from these branches. It is therefore unlikely that the angle of branching is closely associated with the cause of the lesions. The striate and pontine vessels have in common the fact that their diameters at their origin from the parent vessel and at their entrance into the brain substance are the same. These arteries have no extracerebral anastomoses. On the other hand, the extracerebral anastomoses so much stressed by the early authors are probably of importance when the anastomoses occur between vessels of the right and left side. Areas receiving such a double supply are extremely resistant to circulatory disturbance. As examples may be cited the spinal cord, colliculi, hypothalamic nuclei, and cortical areas adjoining the corpus callosum. The multiple ramifications of the cortical arteries, in contrast to the striate and pontine arteries, may cause the blood pressure to be "stepped down" gradually, as Boyd expresses it.

Regarding the intracerebral angioarchitecture of the areas most frequently affected, very little is known. Unfortunately Pfeiffer's (1928) method has not been applied to the human brain stem yet. Ludlum (1909) mentions that most of the infarctions formed in his cases occurred in the boundary zones of two different arteries. In the pons, areas which are supplied by one terminal artery are more often affected than those which are supplied by many small terminal arteries (Stern, 1935). Further investigations in this direction are necessary, more especially as Pfeiffer's method gives a more accurate picture of the intracerebral precapillary anastomoses.

As our knowledge of the embryological development of the cerebral vessels is still rudimentary, it is not possible to decide if the areas of high vulnerability represent areas in which minute developmental abnormalities more commonly occur. Oberndorfer (1928) recorded finding, in identical twins suffering from whooping-cough, hæmorrhages in almost the same place in the frontal lobe. In such cases microscopical developmental abnormalities of the vessels as described by Elkington (1935) may cause a local diminution of resistance to circulatory overstrain. In discussing local vulnerability mention should be made of the developmental anomalies in the walls of the cerebral vessels giving rise to "congenital" aneurysms (Fearnsides, 1916; Forbus, 1930). As these abnormalities are of greater importance in discussing the pathogenesis of subarachnoidal than of cerebral hæmorrhage, no further mention of them shall be made here. It is doubtful if the occurrence of congenital anomalies of the circle of Willis, such as hypoplasia or congenital obliteration of the posterior communicating artery found in arteriosclerotic brains with softenings and hæmorrhages are actually of as much pathogenetic importance as Saphir (1935) suggests. As these anomalies may frequently be found in otherwise healthy brains, the cases described by Saphir seem to represent a coincidence. In cases of hypertension occurring in acute, subacute, and chronic Bright's disease (Stern, 1935) the area of the basilar artery seems to be more often affected than other areas. This finding may be related to cerebral œdema or rapid increase of intracranial pressure, for hæmorrhages and softenings may be found in the branches of the basilar artery in brain tumours (Rosenhagen, 1932; Bannwarth, 1935), sunstroke (Stern, 1933), apoplectic ventricular hæmorrhage (Altwater, 1911; Greenacre, 1916), and cerebral injury (Duret, 1919). There are different theories to explain this, none of which is as yet sufficiently substantiated. Duret thought that a sudden displacement of cerebrospinal fluid by increased intracranial pressure compresses the vicinity of the aqueduct. Kolisko

(1911) pointed out that the basilar artery as it lies parallel to a bony surface is more exposed to the mechanical effect of increased pressure than other basal arteries. Greenacre (1916) put forward the theory that there must be some mechanism regulating the flow of blood to the brain through the carotid and vertebral systems respectively. As the result of massive ventricular hæmorrhage the mechanism becomes disturbed, and as a result a backflow of blood within the circle of Willis may take place. Wilson and Winkelmann (1926), who examined cases of pontine hæmorrhage occurring in different kinds of cerebral disease, pointed out the mechanical way in which the pons was exposed to damage by increased intracranial pressure. As our knowledge of the physiology of cerebral circulation is still incomplete, the problem of local vulnerability must await advances in physiology.

Conclusions

In a review of the pathology of cerebral apoplexy it is not possible to summarize the many facts which have been found or the theories which have been put forward to explain these facts. Surveying the development of the research on the subject of apoplexies the impression is obtained that a limit has been reached which purely descriptive investigation cannot pass. At least the morphology of the cerebral lesions found in apoplexy seems complete. It has been shown that the original mechanical conception of the early authors had to be abandoned in view of more recent findings, e.g. it now appears that cerebral softenings are not necessarily the result of physical obstruction of the arteries, and the theory that cerebral hæmorrhage is due to rupture of rigid or deformed vessels by internal strain is not sufficiently supported by facts. But such statements are essentially negative. The existence of a large number of different theories merely proves that none of them is adequate to explain all the facts. When the knowledge of the physiology of intracranial circulation has proceeded further a better explanation of events may be available. Nevertheless there are some points which may still be solved by a study of morphology. The rôle of the veins in the pathogenesis of apoplexy has been much neglected, due in part to the fact that little is known about the normal anatomy of the intracerebral veins. It is to be noted that the work of Pfeiffer has shown that the arrangement of the veins is essentially different in various parts of the cerebrum. This arrangement and the presence of many precapillary anastomoses in the brain make it necessary to re-investigate the subject from the angle of a study of the angioarchitecture of the brain.

An important point worthy of study is to determine if there is a close relationship between the character and the site of the lesion on one hand and the ætiology on the other. Already some work in this direction has been done by recent investigators. It appears probable that investigations directed to correlate the different clinical forms of hypertension and the pathology of the brain may prove fruitful. Further, as abnormalities in embryological development of the cerebral vessels appear to offer an explanation for the predilection of certain sites for hæmorrhage, a more intimate embryological study may be undertaken with advantage.

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